UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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CARDIOVASCULAR AND RENAL DRUGS

ADVISORY COMMITTEE

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94th MEETING

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THURSDAY,

OCTOBER 11, 2001

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ORIGINAL

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service. According to the Food and Drug Administration makes no representation as to its accuracy.

The Advisory Committee met in Building 10, Clinical Center, Jack Masur Auditorium, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland, at 9:00 a.m., Jeffrey Borer, M.D., Acting Chairman, presiding.

PRESENT:

JEFFREY BORER, M.D., Acting Chairman

JOAN C. STANDAERT, Executive Secretary

PAUL ARMSTRONG, M.D., Member

MICHAEL F. ARTMAN, M.D., Member

PRESENT: (cont.)

THOMAS FLEMING, Ph.D., Member

ALAN T. HIRSCH, M.D., Member

JoANN LINDENFELD, M.D., Member

STEVEN NISSEN, M.D., F.A.C.C., Member

Gloria
~~GLOREA~~ ANDERSON, Ph.D., Voting SGE Consultant

RAYMOND LIPICKY, FDA

ALSO PRESENT:

PETER CARSON, M.D. (Novartis)

JAY N. COHN, M.D. (Novartis)

LLOYD FISHER, Ph.D. (Novartis)

ROBERT GLAZER, M.D. (Novartis)

MATHIAS HUKKELHOVEN, Ph.D. (Novartis)

JAMES HUNG (FDA)

MALCOLM MACNAB (Novartis)

Sheri
~~SHERRY~~ TARGUM (FDA)

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(8:58 a.m.)

ACTING CHAIRMAN BORER: I'd like to call this meeting to order.

This is the 94th meeting of the Cardiovascular and Renal Drugs Advisory Committee.

We have a conflict of interest statement to be presented by Joan Standaert, and then I have a couple of opening comments about the format today.

Joan.

MS. STANDAERT: The following announcement addresses conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 USC 208(b)(3), a full waiver has been granted to Dr. Thomas R. Fleming. A copy of this waiver statement may be obtained by submitting a written request to the agency's Freedom

of Information Office, Room 12A-30, Parklawn Building.

In addition, we would like to disclose for the record that Dr. Paul W. Armstrong has an interest which does not constitute a financial interest within the meaning of 18 USC 208(a), but which could create the appearance of a conflict.

The agency has determined notwithstanding this interest that the interest of the government in his participation outweighs the concern that the integrity of the agency's programs and operations may be compromised.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

That concludes the conflict of interest statement for October the 11th.

ACTING CHAIRMAN BORER: Okay. I'm going to first ask if there are any comments from the

public. The meeting is open for public comment.

(No response.)

ACTING CHAIRMAN BORER: Okay. If there is no comment, we'll move on.

I want to point out that the schedule as denoted here on the agenda shows a 3:00 p.m. adjournment time. We're going to try to move ahead reasonably efficiently to meet that adjournment time because of the extraordinary problems that now exist with regard to air travel and the extended time that some of our committee members need to be able to reach their planes in order that they don't have to stay an extra night.

It shouldn't be a problem if we stick to the schedule. So it may be that at some point I'll cut off discussion not arbitrarily, but only so that we can stay within our agenda.

In addition, you'll notice that there's a change in the alignment of the end table here. The only reason for that is so that I as the Chairman can see all of the committee members and not exclude them from commenting in the appropriate way at the appropriate time.

With that having been said, we'll begin the discussion of Diovan (valsartan) for the

indication of treatment of patients with congestive heart failure. The sponsor is Novartis Pharmaceuticals Corporation, and the presentations will be introduced by Novartis by Dr. Mathias Hukkelhoven, Vice President for Regulatory Affairs.

DR. HUKKELHOVEN: Dr. Borer, Dr. Lipicky, members of the Advisory Committee, FDA, and guests, good morning. My name is Mat Hukkelhoven. I am Vice President of Regulatory Affairs for Novartis Pharmaceuticals Corporation.

On behalf of Novartis, I would like to thank you for this opportunity to present and review Diovan data for a new indication, the treatment of heart failure.

Diovan or valsartan is an angiotensin receptor blocking agent acting on the AT-1 receptor subtype. It was approved in 1996 for the treatment of hypertension, and it has been widely prescribed since that time. It is now available in over 80 countries.

We are pleased that we are able to present data which demonstrates clinical benefit with Diovan in treating patients with heart failure. Diovan is the first angiotensin receptor blocking agent to achieve such results. These beneficial results were achieved on top of a background regimen that included

an assortment of approved drugs for each participating patient as prescribed by their physician.

Our development program for the new heart failure indication consists of several studies. Val-HeFT or Protocol 107 is a key morbidity/mortality trial involving approximately 5,000 patients, and it was conducted at 302 centers in 16 countries.

In addition, we also conducted four shorter term control studies, Protocols 103, 104, 106, and 110. These studies evaluated a variety of endpoints other than morbidity/mortality, including quality of life.

Our clinical program was developed in consultation with the FDA. Importantly it was agreed that the Val-HeFT study could employ two primary endpoints, and a positive outcome for either would support an application. The two primary endpoints are all cause mortality and the combined endpoint of morbidity and mortality.

Based on our clinical results, the following profile emerges. Diovan improves morbidity since it reduced hospitalizations for heart failure. It slows the progression of heart failure. It improves the New York Heart Association functional class rating and ejection fraction. It improves signs

and symptoms of heart failure, and it improves quality of life versus placebo.

The most common adverse experiences were dizziness and hypotension.

We propose the following draft indication statement based on our data. Diovan is indicated for the treatment of heart failure, NYHA Class II to IV, in patients receiving usual therapy, such as diuretics, digitalis and either ACE inhibitors or beta blockers. Presence of all these standard therapies is not mandatory.

Our discussions this morning pertain solely to a new indication for congestive heart failure. Dr. Jay Cohn will discuss the efficacy of Diovan in treating patients with heart failure. Dr. Cohn is Professor of Medicine at the University of Minnesota, and he serves as the study chairman for our Val-HeFT trial.

Dr. Robert Glazer will then summarize the safety of Diovan in heart failure patients. Dr. Glazer is Director of Cardiovascular Clinical Research at Novartis.

Dr. Cohn will then return to summarize our perspectives of risk-benefit in this indication.

In addition to the speakers this morning,

we have the following advisors who are available to answer specific questions the committee may have: Dr. Peter Carson, Associate Professor of Medicine at Georgetown University and Chairman of the Endpoint Committee, if and when he arrives; and Dr. lloyd Fisher, Professor Emeritus at the University of Washington.

I would now like to ask Dr. Cohn to the podium.

Thank you.

DR. COHN: Thank you, Mathias.

Dr. Borer, Dr. Lipicky, members of the committee, it's a pleasure for me to be able to share with you this morning the data supporting the use of valsartan in the management of heart failure.

Let me provide you a little background for a moment on why we are here today. The management of heart failure has undergone considerable changes in recent years.

The pointer is where? There should be a pointer here somewhere, but that's all right.

As you can see from this first slide, there has been quite a development of drugs for the management of heart failure over the last -- thank you -- over the last 15 years or so, beginning with the

first demonstration that nitrate and hydralazine could alter the course of heart failure. That was the first clinical trial carried out in heart failure.

And then subsequently the ACE inhibitors were assessed initially in Class IV heart failure and subsequently in more moderate heart failure, Class II and Class III, demonstrating efficacy on the long-term outcome.

Subsequently there were data to support the use of beta blockers beginning in around 1996. In 1999, a single study demonstrated that spironolactone had a favorable effect in very severe heart failure. That has never been submitted to the FDA for evaluation.

And most recently, the demonstration that one could achieve benefit with biventricular pacing.

So there has been a considerable expansion of our therapeutic armamentarium over these years.

Now, the rationale for an angiotensin receptor blocker is, I think, well known certainly to the committee. It's widely appreciated that angiotensin exerts a variety of adverse effects both on the vasculature and on the heart and on neural hormonal system that may contribute to progression of heart failure.

Traditionally, we have used ACE inhibitors in an effort to inhibit the formation of angiotensin II, and that was, indeed, the concept over the years that we've been widely using ACE inhibitors to treat heart failure, but it's becoming increasingly apparent in recent years that ACE inhibitors given certainly in the doses that are currently used clinically does not suppress very effectively the formation of angiotensin II, and that a good deal of the efficacy of ACE inhibitors may be related to its preservation of bradykinin by inhibition of the breakdown of bradykinin, and that bradykinin nitric oxide system may be an important contributor to the long-term benefits of ACE inhibitors.

Thus, if angiotensin II still persists, and it may well also persist because of the activity of alternate pathways to formation, particularly the chymase (phonetic) system which is active in tissues, then we still may have circulating in tissue levels of angiotensin II which interact with the AT-1 receptor to subserve vasoconstriction, vascular and cardiac growth, and adverse consequences in the syndrome of heart failure, and this, of course, is where the angiotensin receptor blockers, such as valsartan, which are specific inhibitors of the AT-1 receptor,

might further block the renin angiotensin system which we believe has deleterious effects in heart failure.

Now, what I'm going to present to you today is the clinical development program for valsartan in heart failure, and as Mathias has already described to you, there are four preliminary studies that were done that led to the major outcome trial called Val-HeFT that will spend most of the time this morning discussing.

Study 103 and 104 were sort of proof of concept studies, that is, can one get a hemodynamic effect when one administers valsartan in patients with heart failure.

Hemodynamics do not serve as an adequate surrogate for long-term efficacy of drugs in heart failure. They may well serve as a target for acute interventions because there is an acute response to hemodynamic response, which will influence acute symptoms. But the long-term course of the disease cannot really be predicted by hemodynamic effects of the drug.

Nonetheless, it is often important, particularly if you're using your drug with a known hemodynamic effect, that we demonstrate that the drug is exerting this predicted effect in patients with

heart failure.

So two trials were done. Study 103 was a trial in patients receiving neither ACE inhibitors nor beta blockers, and this was carried out in Russia, and it was placebo controlled and also lisinopril controlled, and there were -- and I'll show you the data on valsartan dosing -- there were 116 patients in this trial. It was of four weeks' duration, and the major primary endpoint was hemodynamic effects from right heart catheterization.

Study 104 was carried out in the United States and Veterans Affairs hospitals. The patients were all mandated to be on ACE inhibitor, and they were on ACE inhibitor in doses that are recommended from the large scale trials.

They could not be on beta blockers, and there was a placebo controlled assessment of four weeks' duration of administration of valsartan in two doses in 83 patients.

Study 106 was an exercise tolerance treadmill exercise study, and as I'll suggest to you in a moment, exercise, again, is not a very useful surrogate marker for long-term efficacy, but it's one of the kinds of endpoints that one often carries -- attempts to study.

These patients were allowed to be on ACE inhibitors and beta blockers, and the vast majority were receiving ACE inhibitors, and about a third of them were receiving beta blockers. There were 770 patients in this trial. It was a 16 week study, and the primary endpoint was exercise tolerance.

Study 110 was a study in which patients were not allowed to be on ACE inhibitors during the trial, but they had been on ACE inhibitors, most of them, until the randomization date. They were also allowed to be on beta blockers, and about 30 percent of them were on beta blockers.

And it was a comparison between enalapril and valsartan in patients who had been on an ACE inhibitor up until the day of randomization. So it's a protocol that basically asks the question: will valsartan exert the same benefit as continuing an ACE inhibitor in patients with heart failure?

And it was a six minute walk test, a 12 week duration study.

And then Val-HeFT, which will spend most of the time on, was carried out in 5,010 patients, and it was a morbidity/mortality trial, but in addition, there was a substudy in which a walk test was assessed.

Now, this is the study design of the two hemodynamic trials, Studies 103 and 104. This is the study in Russia. This is the study in the United States.

The Russian study examined three different dose levels of valsartan, 40, 80, and 160 milligrams twice daily, and they compared that to lisinopril, which was titrated up to ten milligrams a day, and there was a placebo group, and after a run-in the patients were randomly assigned to these five different treatment groups and followed for 28 days. They were catheterized at day zero and again at day 28 to assess hemodynamic effects.

Study 104 used two different doses, 80 and 160 twice daily versus placebo, and these patients, once again reminding you, were all on ACE inhibitor. None of these patients were on an ACE inhibitor prior to randomization.

These are the hemodynamic data in Study 103. The placebo group is in green. At the left are the bars at day zero, four to eight hours after administration of the drug. The values were meaned over that 48 hour period.

On day 28 assessments were carried out at zero time. That is, before drug was administered the

patients had been on chronic therapy, and then the third set of bars is 12 hours after the dose was administered on day 28.

In green is the placebo group, and you can see very little change in pulmonary capillary wedge pressure during the follow-up period, and the little increase here.

The three valsartan doses are shown here, 40, 80 and 160 milligrams twice daily, and this is lisinopril, and you can see there is a clear hemodynamic effect of valsartan and probably also of lisinopril compared to placebo. These are least mean squares and some of the values are statistically significant and some not.

This is Study 104, and this again is the pulmonary capillary wedge pressure. Now the unique feature of Study 104 is that at zero time, patients were given a dose of lisinopril to maintain full ACE inhibitor effect throughout the study duration. So they got lisinopril here, and they got lisinopril again here before a dose was administered on day zero and day 28.

So the placebo effect in green is really a lisinopril effect in patients on chronic ACE inhibitor therapy, and then in addition to lisinopril,

the valsartan patients were given valsartan 80 or valsartan 160, and what one sees is a trend for a dose response to valsartan, that is, a great reduction in pulmonary capillary wedge pressure here on day zero, here on day 28, and again on day 28, hour 12, there isn't much difference between lisinopril and the drug.

We also looked at diastolic pulmonary artery pressure because some patients didn't get their wedge pressure measured, and once again, a dose dependent reduction of pulmonary -- PA diastolic pressure.

This is systemic blood pressure, systolic blood pressure. Again, the appearance of a dose dependent reduction of blood pressure.

Now, we also measured hormones in Study 104, and this was plasma aldosterone levels. Plasma aldosterone levels were strikingly reduced with both doses of valsartan compared to lisinopril and appeared to be a bit of a dose dependent effect here.

And plasma norepinephrine also exhibited some decline in perhaps a dose dependent fashion, and in all of these studies, the one 60 milligram twice daily dose of valsartan exerted the greater hemodynamic effect. So that was the dose that was selected to be introduced into Val-HeFT when we

designed Val-HeFT.

Now, the exercise studies I will review briefly for you. As I've already suggested, exercise tolerance, that is, treadmill exercise and six minute walk tests, have not served as a very reliable guide to efficacy and heart failure, but these studies were carried out just to determine if there was any demonstrable effect from valsartan.

This is the trial, 106 trial with treadmill exercise, and there were three different doses of valsartan studied in that trial versus placebo.

Remember most of these patients were on an ACE inhibitor, and somewhere over a third of them were on a beta blocker. There was no demonstrable difference among the four treatment groups on change in exercise performance and the p values were not significant. So no demonstrable additional exercise improvement when valsartan was added to background therapy.

And these are the two six minute walk tests. This is a substudy from Val-HeFT, and I put it in here because it was an exercise study. There were 633 patients in that substudy. There was really no striking change in six minute walk tests, essentially

equal between the placebo and valsartan groups.

And this is Study 110, which was a six minute walk test. Now, this was a positive control study because it was valsartan versus enalapril in patients previously on an ACE inhibitor. There were 134 patients in this trial, and there was no difference at least between enalapril and valsartan. In fact, the trend was for a little greater improvement with valsartan than enalapril, but nowhere near statistically significant. So those studies are basically a wash.

Well, now let me go into the Val-HeFT protocol with you to review what we have done. This was the design of Val-HeFT. Entrance criteria, patients with chronic stable heart failure, and they had to have ventricular enlargement both by transverse diameter of the left ventricle at end diastole that is greater than 2.9 centimeters per meter squared, and by an echo ejection fraction of less than 40 percent, and they all had to be in New York Heart Class II to IV for eligibility in the trial.

Now, each of the echo labs that participated in this study were validated for their ability to both perform and read an echo, and it was a monstrous undertaking, I can assure you. Many of

the centers were offended by the fact that they had to send three echoes in and demonstrate that they could do it right.

And I can assure you that most of them did not do it right, and the core laboratories that oversaw the echo quality had to go back and reeducate echo technicians and readers as to the importance of precision in the performance of the test.

They all eventually met the criteria, and we also monitored the quality control throughout by randomly collecting echoes and submitting them through our core laboratory. So we did the best we could do in a multi-center study without having all the echoes read in a single core lab, which would have been an unbelievable burden.

So these were the entrance criteria by echo, and then the patients were randomized. They stayed on their prescribed therapy, and we encouraged all of the physicians to get patients on optimal therapy for heart failure, and then they were randomized to receive valsartan 40 milligrams twice daily, which was titrated at two week intervals. It was a forced titration to 160 twice daily unless there were adverse events along the way that inhibited progressive titration, and I'll show you the data on

that.

And then double blind placebo therapy in the other group, and we followed the patients. All of the patients were followed until 906 deaths were reported, and I'll show you how that figure was arrived at.

There were two primary efficacy endpoints as Mathias has already discussed to you. One was mortality, that is, the time to death, survival curves, and the other was a combined endpoint which we called morbidity, but it included mortality, all cause mortality. Plus episodes of sudden death with resuscitation were called an endpoint.

Patients who were not hospitalized, but needed therapeutic doses of intravenous inotropic or vasodilating agents for four hours out of hospital, that was equivalent we thought to a hospitalization, and that was counted as an endpoint. And the other one was hospitalization for heart failure.

In all of these events, the death and all the other primary endpoint events, were adjudicated by an endpoint committee, and they reviewed every one of the hospitalizations until a patient was identified to have had a hospitalization for heart failure, which gave them an endpoint for the trial. So this was a

burdensome effort as well, but we thought it was very important to do.

Now, here were the statistical considerations in Val-HeFT. Since we had two endpoints, we divided our alpha into two and, therefore, assigned an alpha of a .025 to both morbidity and mortality.

The mortality alpha was further reduced by the interim analysis carried out by the Data Safety and Monitoring Board using the O'Brien-Fleming method, and that then came down to .02 as the level of significance.

The assumption of the sample size was based on a predicted placebo death rate of 12 percent per year. We didn't achieve that. It was nine percent. So in a way, we were under powered from the very beginning because the mortality rate was lower than we had predicted.

We were trying to identify a reduction in mortality of 20 percent with a 90 percent power and a two-sided significance of .025, and that's how we came up with the need for 906 events in order to achieve our target.

All patients were followed to the study end. They were censored obviously at the end of the

study. At the time of loss to follow-up, and I can tell you that you'll see in a moment that there were very few of those, and at the time of heart transplant. So those were the censoring criteria.

There was an endpoints committee, as I pointed out that, reviewed all of the endpoints, and there was semi-annual interim analysis by the DSMB.

Patients were all over 18 years of age. They had chronic stable heart failure, and as I pointed out, their ejection fraction less than 40 percent and their left ventricle larger than 2.9 centimeters per meter squared.

For those of you who aren't used to the index, LVIDD, this means left ventricle well over 5.5, and usually over six centimeters in the trial.

And they all had to be on a stable regimen of prescribed heart failure therapy for at least four to six weeks prior to randomization.

The usual exclusion criteria, patients with significant valvular, obstructive valvular disease, patients with recent ischemic episodes or CVAs or recent reperfusion therapy, patients likely to need bypass or reperfusion in the near future. People with rapidly deteriorating heart failure were excluded. Those on the transplant list were excluded.

Those with predominant right heart failure due to pulmonary disease were excluded, and those on drugs which we felt were contraindicated, such as Class IC anti-arrhythmics, patients who required IV inotropes or IV vasodilators in the previous three months.

There were 302 centers in 16 countries that participated in the trial, and this is the breakdown of the number of patients entered from each of these various sites. The United States entered a little less than 50 percent of the patients, and you can see the big contributors outside the U.S., Italy, the Netherlands, Germany, et cetera.

The follow-up averaged 699 days in both treatment groups. The mean daily dose of valsartan administered was 254 milligrams. Remember 320 would have been the target dose so that we came pretty close.

The mean dose of placebo was just slightly higher, 283.

The duration of treatment in days was somewhere over 600 days on average between the two groups, and 84 percent of the valsartan patients and 92.7 percent of the placebo patients achieved the target dose, which is, I think, pretty remarkable. This is a high dose of valsartan, and yet the vast

majority of patients achieved that target dose.

Here's the disposition of the patients. Ninety-nine percent of them completed the trial either to death or a trial endpoint. Premature trial termination in the absence of death occurred in only a small number of patients, one percent in both groups; a small number of heart transplants, 18 and 23; loss to follow-up. I think this is a tribute to the quality of the performance of this trial. Three and four patients lost to follow-up out of 5,010. A few withdrew consent.

Four hundred and 48 or 18 percent of the valsartan patients and 14 percent of the placebo patients stayed in the trial, but discontinued trial treatment. Again, I think a very acceptable number.

The majority of those, the difference between the two was related to intolerable adverse experience, nine percent in valsartan, five percent in placebo.

Here are the baseline characteristics of the patients. There were 2,511 in the valsartan treated group and 2,499 in placebo. They averaged about 63 years in age. Eighty percent were male. Ninety percent were white.

We have an unfortunately small

representation of black patients. Some of these are South African blacks, and a slightly larger fraction are African Americans. It is too small a group to make many conclusions about, and there was a small number of other racial groups identified.

Coronary disease was the etiology of the heart failure in about 57 percent of the patients. Thirty-one percent were identified as having idiopathic cardiomyopathy, and the causes are shown here.

Sixty-two percent of the patients were in Class II heart failure, 36 percent in Class III, and a small number of Class IV patients.

The ejection fraction averaged about 27 percent. The left ventricle was 3.6 centimeters per meter squared body surface area. So these are large ventricles.

The blood pressure, 124 over 76, and here was their background therapy, and this is going to become of some importance as we go through these data. Eighty-six percent of the patients were on a diuretic. Two thirds were taking digoxin. Thirty-five percent were on a beta blocker, and 93 percent on an ACE inhibitor.

Now, this was far higher than we see in

the practice of medicine in the community today, and remember one reason for that is the patients who are on an ARB were excluded from participation, and even though there are no data yet, there are many physicians who are substituting ARBs for ACE inhibitors because their patients coughed once.

And consequently those patients were excluded. So these are patients who are largely on ACE inhibitors, and only seven percent were not on an ACE inhibitor, and that's an important group, too.

Their quality of life was assessed by the Minnesota living with heart failure questionnaire, and the overall average score was about 32, which by the criteria of that questionnaire puts them in the moderate heart failure range, not severe, but not mild either, and that's broken down by the emotional and physical component of that Minnesota form.

Well, what kind of doses of ACE inhibitors were they on at baseline? And this is the list of ACE inhibitors that were being used. Remember these are physician choice.

The three biggest ACE inhibitors in use were enalapril, lisinopril, and captopril. The doses of these drugs are very close to the recommended doses. For enalapril and lisinopril, very close to

the 20 milligram dose which is generally recommended daily dose. Captopril, probably lower than one would have chosen to use in clinical trials, but obviously this drug is often used more than once a day, and the mean dose was about 80 milligrams, and the other is incomparable doses.

What about the beta blockers being used? Well, the two most commonly employed beta blockers were carvedilol and metoprolol, and they were used in doses which are probably lower than one would choose based upon clinical trial data, but this is the real world, and I see patients coming referred to me on beta blockers, and for the most part, they're on low doses.

There's some concern about titrating up to the doses that have been used in most clinical trials, and then the other beta blocker uses are shown below.

Well, this was the primary endpoint of Val-HeFT. These are the two primary endpoints. Mortality was identical in the two treatment groups, a hazard ratio of 1.02.

The morbidity endpoint, which of course includes mortality, exhibited a striking reduction in the valsartan group compared to the placebo group, a hazard ratio of .87, a p value of .009.

So the study achieved its target endpoint with one of the two primary endpoints.

Here is the Kaplan Meier survival curve exhibiting superimposition of the placebo and valsartan arms over 30 months of follow-up.

And what about mechanism of death? These were all adjudicated by our endpoint committee, and you will see there's very little difference between the valsartan and placebo groups. Sudden death here, pump failure death here, sudden death with per monitory worsening of symptoms, other vascular causes, non-cardiovascular deaths very similar.

So there appeared to be no mechanistic difference in what led to death in the two treatment arms.

Here is the Kaplan-Meier curve for morbidity, which exhibits separation beginning at about three months and then widening over time. Once again, this was a 13.2 percent risk reduction, and the p value was .00852.

Now, in the morbidity endpoint, obviously we had four different possible contributors to morbidity, and here is the breakdown of those four contributors. The biggest difference was heart failure hospitalization occurring at 18.2 percent of

the placebo group and 13.8 percent of the valsartan group, and that leads us to do an analysis of hospitalizations in more detail.

Here were the cardiovascular deaths, which are very similar. Here's the first nonfatal morbid event exhibiting a striking reduction in the valsartan arm, first heart failure hospitalization, a similar reduction of hazard ratio to .725. The first sudden death with resuscitation, very small numbers so not too meaningful.

This is the curve for incidence of worsening heart failure. Now, one has to censor deaths when one does this kind of an analysis, but it gives you some idea about the frequency in which patients are hospitalized for heart failure as an initial event, and you can see that the curves begin to separate at about three months ago, and they widen over time.

This is a 27.5 percent risk reduction, and the p value for that is .00001.

Now, the agency had raised some issues about overall cause hospitalizations, and let me just provide you that data because I think there's been a bit of a confusion about that.

Heart failure hospitalizations, now these

are investigator assessed because all the endpoint committee did was to adjudicate the first heart failure hospitalization. Once a patient had been hospitalized for heart failure, they no longer adjudicated hospitalizations.

But of course, hospitalizations occurred, and the investigator was busy assessing hospitalizations; the investigators were doing this on their own.

Well, what did the investigators find about heart failure hospitalizations? Well, the investigators identified 266 fewer hospitalizations in the valsartan group compared to the placebo group. This was all cause hospitalizations, a similar reduction. So this is statistically significant. This is obviously not because it is influenced by a large number of non-heart failure hospitalizations which were equal in the two groups.

So this is a tribute in our decision to adjudicate heart failure hospitalizations as an endpoint for the trial. They had no reason to think that valsartan would reduce the number of other hospitalizations, but we hoped it would reduce heart failure hospitalizations and not increase non-heart failure hospitalizations, and that's indeed what we

found.

Now, there's also been some question raised about the days in the hospital. Not only are we interested in how many patients get hospitalized or how frequently they're hospitalized, but what about the number of days in the hospital?

Well, highly significant reduction of days in hospital, mean days in hospital during the trial, 3.5 for valsartan compared to 4.8 for placebo. All cause hospitalizations also tend to be reduced, not quite significant, and non-heart failure hospitalizations once again, identical.

Well, what about days alive and out of the hospital? Well, this is an attempt to get at that. This is not an easy number to get at, but once again, as you might expect, there's more days out of the hospital and alive in the valsartan treated group than in the placebo group. And these are, again, the data I showed on the previous slide.

Well, you can't do a statistic on that very easily because the number of days out of the hospital, alive and out of the hospital, varies tremendously based on when the patients were entered into the trial because there's a wide range of duration of follow-up. So you get this wide standard

deviation, and then you get a p value which, of course, is nowhere near significant.

So it's important to correct the number of days alive and out of hospital for the number of years of follow-up or months of follow-up, and we've done that on this slide. And this is the mean days per year alive and out of hospital, and now, of course, the standard deviation gets much lower, and the heart failure days in hospital is highly significant. All cause is not, and of course, non-heart failure remains essentially identical.

Well, we monitored a number of secondary endpoints. Signs and symptoms of heart failure were assessed by the investigator, and new York heart class was assessed, and this is the change from baseline to endpoint in each patient of these measurements.

Here's New York heart class. More patients with valsartan improved and fewer worsened than in the placebo group, and that was highly significant, .001, and that's true also of jugular venous distention, of edema, of rales, not quite of third heart sound, of paroxysmal nocturnal dyspnea, of dyspnea at rest, dyspnea on effort, fatigue, and not quite orthopnea.

This is actually a remarkable

demonstration of efficacy. I've never seen a trial before in which all of these secondary endpoints exhibited a benefit from a drug. It's hard to come up with this kind of data, and so this was remarkably congruent.

DR. FLEMING: Could I just -- you're making a key point. If we could go back, Jay, if I could just interrupt you for a second.

DR. COHN: Sure, by all means. I love to be interrupted, Tom. So don't hesitate.

DR. FLEMING: When you point out how remarkably congruent it is, I look at that and wonder as a statistician if it's even more congruent than random chance would anticipate. Yes, these are all significant. They all show about a one to three percent more favorable result in the percent that improve and a one to three percent more favorable result in the number that worsen, almost exactly the same across all of these endpoints.

There must be a lot of correlation between these endpoints.

DR. COHN: Well, sure, there are. New York heart class and symptoms all go together. Jugular venous distension is an observation which shouldn't really relate to such things as fatigue or

dyspnea, but they are all going to go sort of together, and your point being then what?

DR. FLEMING: My point being addressing your point that it was remarkable that they were all significant. Well, if in fact you have a general quality of life phenomenon and you have many variations of measuring the same phenomenon, then I would expect a consistency and significance across those results. It's not as though we have 13 independent assessments all of which --

DR. COHN: Oh, no.

DR. FLEMING: -- achieve a p of .001.

DR. COHN: I would agree. I was just commenting on the fact that in other trials, and I've been involved in a lot of other trials, it's been very hard to actually demonstrate any clinical benefit on these kinds of clinical measurements, and we were able to do it in this study on all of them.

But your point is well taken that they are mutually dependent in many respects. So you might expect them to go together.

This is the Minnesota living with heart failure questionnaire. Now, this is filled out by the patient. All the other data are obtained by the physician, the physician's assessment. This is the

patient filling out a form. This form is completed when the patient walks in the door before they meet with the health care provider.

So they sit down and they fill out this 21 question form. So it's very independent kind of assessment before they've been influenced by meeting with the nurse or the doctor.

And the primary endpoint was the change from baseline to endpoint, whenever the endpoint occurred, and the patients on placebo exhibited a progressive worsening of their quality of life. A rise in score means quality of life has become worse. The patients on valsartan did not exhibit that worsening. So the overall score was highly significantly favorable for valsartan.

Now, this score is traditionally broken down into two components. I must point out to you that this overall score has been heavily validated in a number of trials. The breakdown into emotional and physical is not as well validated, but nonetheless, there are a group of questions which are defined as the physical score and another group defined as the emotional score, and there was a similarity in the benefit of valsartan, perhaps more dramatically with the physical score which you might have expected.

This is the time course of quality of life over the 30 months of the trial. Assessments were made at four, 12, 18, 24, and 30 months, and you can see that in the first few months there was a tendency for an improvement in quality of life, not really different between the two, and at 12 months not really much different.

But by two years, there was a significant difference. At the endpoint, again, out here, the trend was even greater. None of these were quite independently statistically significant, but the endpoint was, and that was the prescribed endpoint for the trial, was baseline to endpoint, and whenever the patients ended, they were assessed.

Now, ejection fraction was monitored by echo, and these are the ejection fraction data from baseline to endpoint. The valsartan group exhibited a rise of about four units of ejection fraction. The placebo group, a rise of about three units. It's a small difference, but highly significant.

And this is the sequential changes in ejection fraction over time. By four months there was already a difference; 12 month, 18, 24, and 30 months. In all of these time frames, the valsartan group exhibited a greater rise in ejection fraction than the

placebo group.

Now, I must tell you that this increase in ejection fraction in the placebo arm is not consistent with previous data. We've monitored in the Val-HeFT trials. The placebo group goes down.

Yeah, Jeff.

ACTING CHAIRMAN BORER: Well, I wondered about this, too, but all of these people are on background therapy.

DR. COHN: Exactly.

ACTING CHAIRMAN BORER: That affects EF over time.

DR. COHN: And, in fact, as you will probably see later on -- I think I have a slide that shows it -- the group on beta blocker, we did not prescribe that they had to be on beta blocker for, say, more than six months before they're randomized. So what you will see in the beta blocker treatment is a tendency for an ejection fraction to go up during the course of the trial from the beta blocker itself. So this is a very well treated group, and I suspect the rise in EF reflects the effect of other drugs.

But that's the way the data came out, and it was certainly a significant benefit of valsartan.

Now, we also did ejection fraction Study

106 just to show congruence because here we have three different doses of valsartan, 40, 80, and 160, and here was the placebo group, and you can see in Study 106, all three doses seem to improve EF more than the placebo.

Once again, it does look like 160 was the more effective dose. So we were reassured that we probably did use the right dose in Val-HeFT.

Now, we also monitored left ventricular chamber dimension by echo, and this is the change from baseline to endpoint of left ventricular internal dimension in diastole. It went down in the valsartan group, less reduction in the placebo group, the difference very highly significant.

And here is the sequential changes in LVIDD. The reduction was apparent by four months and persisted throughout the trial. So clear evidence for benefit on left ventricular dimensions or remodeling, which I would call that, from valsartan, but modest, not gigantic, but highly significant, a tribute to the large numbers of patients that we were able to monitor.

Now, we also measured neural hormones. This was norepinephrine and BNP levels monitored over time, and the endpoint was baseline; the secondary

endpoint was baseline to the endpoint assessment, and here you can see valsartan prevented the increase in norepinephrine over time that was observed in the placebo group. This is the valsartan group, highly significant difference.

And with BNP, the placebo group rose. The valsartan group fell, and once again, a highly significant difference.

Here are the sequential changes in norepinephrine. They were measured at four months, 12 months, and 24 months, and you can see at each time frame norepinephrine was rising in the placebo group, not in the valsartan group.

And here is BNP once again, a decline in the valsartan group and a progressive increase in the placebo group, again, highly significant differences.

So what can we say from this overall summary of the Val-HeFT data? We can say that valsartan clearly reduced morbidity in patients receiving prescribed therapy for heart failure by 13.2 percent. This was the p value.

It decreased the risk for first heart failure hospitalization by 27.5 percent, and here the p value gave us four zeros before the one.

It improved signs and symptoms of heart

failure. It improved ejection fraction, reduced left ventricular dimension, improved quality of life, and had a favorable effect on norepinephrine and BNP, albeit with similar mortality between the two groups.

Now, let me then just put all of this together with the three placebo controlled preliminary studies, as well as Val-HeFT and review what we have learned about valsartan.

Hemodynamics, I think clear evidence that valsartan is effective on hemodynamics both in the absence of ACE inhibitor and in the presence of ACE inhibitor.

We've determined that valsartan cannot produce further improvement in exercise performance, at least in the modest size studies that we have carried out, in addition to background therapy. In the patients in whom we have monitored signs and symptoms, the Val-HeFT study, they were improved.

Quality of life was improved in the Val-HeFT. Neural hormones were demonstrated to be improved in actually all three of these studies, not determined in 106.

Left ventricular function was monitored in two studies, Val-HeFT and 106, and in both of them the effect was favorable, and of course, the morbidity

trial and mortality trial, Val-HeFT showing a favorable effect on morbidity, but no demonstrable benefit on mortality.

So let me stop there in terms of the overall study, and then we're going to get into subgroup analysis in a few minutes, but I'll be delighted to take any questions from the committee at this time.

ACTING CHAIRMAN BORER: Let's keep the questions to clarification of the data at this point because Jay has the risk-benefit discussion later when we can get into philosophical issues if there are any.

I have one question while everybody is sort of gathering their stuff. If you go back to slide EC-14 --

DR. COHN: EC-14.

ACTING CHAIRMAN BORER: -- yes, this is really a secondary issue, and it's just for clarification purposes because you already made the point, I think, quite correctly that short-term exercise studies don't predict long-term benefit.

But my reading of what we were sent was that an imputation of a zero value was made for people who died when exercise time was determined for this study, and that the determination that the zero value

should be imputed was made after the study was completed.

I don't know when it was made relative to unblinding. I'm sure it was before unblinding, but we weren't told that, and that if you didn't impute the zero value, in fact, the patients on enalapril did better nominally, not significantly, but nominally, than patients on valsartan.

So although this is not the big, burning issue of the day, I'd like a little clarification about that, if you would.

DR. COHN: Yes. I wasn't involved in one of those two studies and the analysis of the substudy. Who can address that?

Tom. Tom is our biostatistician.

MR. CHIANG: Tom Chiang, Novartis.

Yes, the zero imputation has been defined and decided and documented prior to unblinding for analysis, and real data imputation obviously is done after unblinding.

ACTING CHAIRMAN BORER: Well, don't go away yet.

Why did you do that? I mean, I'm just speaking post hoc here. I mean, you have no evidence of a difference in mortality in these groups. So

after the fact one might expect that maybe, you know, you're not affecting death, but we're suggesting that we are affecting heart failure.

Why would you impute a zero value to people who died rather than last value carried forward? I mean, what was the reasoning behind that?

MR. CHIANG: Before unblinding, we don't know mortality would be equal. So we plan a lot of sensitivity analysis, and you know, imputation for patient died, you know, or could not work due to heart failure, you know, was defined.

ACTING CHAIRMAN BORER: Thank you.

Are there any other questions, issues of clarification from the committee? Paul.

DR. ARMSTRONG: Could we look at Slide 37, please?

Jay, I'm trying to understand the sample size here, and it just gives me a repetitive number of the overall study rather than the patients who were hospitalized according to these categories. Can I get the appropriate sample size that lines up with those three categories?

DR. COHN: I'm not sure what you're -- this is the number of patients that were randomized.

DR. ARMSTRONG: Right.

DR. COHN: And this is the mean days in hospital for those 2,511 patients, and just averaged out over the --

DR. ARMSTRONG: But I just want to know how many patients were hospitalized for heart failure.

DR. COHN: Oh, I guess I showed you that on another slide. What was the --

DR. ARMSTRONG: Okay. I couldn't find that.

DR. COHN: Yeah, what's the slide that shows the heart failure hospitalizations?

DR. ARMSTRONG: Thirty-four, EC-34.

DR. COHN: Yeah, this is heart failure hospitalizations, and this is the number of hospitalizations. So it's 1,000 in the valsartan group, and I can't -- you'd have to extrapolate about 1,266.

ACTING CHAIRMAN BORER: You have the exact numbers in EC-34.

DR. COHN: There's 266 more here than here.

ACTING CHAIRMAN BORER: It's 923 against 1,189.

DR. COHN: Yeah, okay.

DR. ARMSTRONG: Nine, twenty-three

against?

ACTING CHAIRMAN BORER: Eleven, eighty-nine.

DR. ARMSTRONG: And, Jeff, you may want to --

ACTING CHAIRMAN BORER: No, that won't help any.

DR. ARMSTRONG: You may want to reserve the issue of adjudication in the process. You may want to reserve that for later.

ACTING CHAIRMAN BORER: No, if you want to know how it was done, let's ask now.

DR. NISSEN: I'm a little confused about the process of adjudication. As I understand from our briefing book, these were brought to the endpoint committee if it was perceived that they were heart failure, but if they --

DR. COHN: No, all hospitalizations were brought to the -- every hospitalization was referred to the endpoint committee, and then they determined whether the hospitalization was from heart failure. They didn't even have available to them the investigator's assessment. They just saw the data for every hospitalization.

So it was a monstrous undertaking as you

can imagine, and then they identified those that they felt were due to worsening heart failure.

DR. NISSEN: Our briefing book suggests that the sponsor screened all hospitalization endpoints, and those that didn't meet endpoint criteria were not submitted to adjudication so that there was some initial adjudication.

And the second point was that I'm confused about overnight stays in the emergency room included in hospitalization. As I understand it, if a patient was in the ER for 12 hours during the day, they would not be categorized as hospitalization, but if they were in the ER for 12 hours overnight, they would be. Can someone help me with that?

Because that's a troublesome issue we all face.

DR. COHN: Bob, do you want to address the process that you used in Novartis?

DR. GLAZER: Robert Glazer, Novartis.

What happened with the documentation that went to the endpoint committee was that clearly cardiovascular events per a serious adverse event report that came to us, and those events that had any question of being cardiovascular were sent to the endpoint committee, and what was sent to the endpoint

committee was the SAE narrative itself, case record forms or case record form printouts, and any hospitalization data that was collected after that, meaning hospital discharge summaries and, if needed, depending on the case, histories and physicals, laboratory data, ECGs, chest X-rays, and progress notes.

For those cases that were clearly non-cardiovascular, for example, an orthopedic problem that the person was being admitted for, a listing was provided with the patient's identifier and the diagnosis from the serious adverse event report form, and that was provided to the endpoint committee chairman.

If at that point in time he requested additional information, that information was provided, and we collected the hospital records.

DR. LINDENFELD: Just to clarify, so a hospitalization recorded by the investigator as hypotension due to over diuresis would not have been reviewed?

DR. GLAZER: Oh, that definitely would have been reviewed because it would have been considered cardiovascular. The key points are things like orthopedic problems, for example. Those were put

into listings, and again, the endpoint committee chairman could ask for additional information.

DR. ARMSTRONG: You'll excuse me for persisting, but again, in our briefing book, there's an addendum to the endpoint manual that defines an admission due to over diuresis or drug toxicity as a hospitalization for reason other than heart failure.

DR. GLAZER: That's right.

DR. ARMSTRONG: So I'm a little confused. Did you --

DR. COHN: Well, they adjudicated those. Those --

DR. ARMSTRONG: So if a patient came in with over diuresis and hypotension or hyperkalemia or some complication we would ordinarily associate with heart failure, it was classified as not heart failure admission?

DR. COHN: Well, the definition for heart failure, maybe we can put up that slide for the definition here while Bob is still there.

The issue was worsening heart failure. So over diuresis is not worsening heart failure. It is a cardiovascular hospitalization.

This was the endpoint committee definition of hospitalization for heart failure. It was

obviously severe collapse, pulmonary edema, symptoms and signs requiring intermittent or continuous IV therapy.

Hospitalization is defined as an overnight stay even if total duration is less than 24 hours. Remember we also included as our primary endpoint more than four hours in an emergency room. So we captured all of those events, but by definition hospitalization is an overnight stay whether it's in the emergency room or elsewhere, but the four hour criteria was also captured.

DR. ARMSTRONG: If you got an inotrope, right?

DR. COHN: If you got an IV diuretic or an inotrope or a vasodilator and you had to stay there for four hours. And there were very few of those, as you saw on that previous. So almost everything was captured by hospitalization.

But the committee made the judgment that if somebody came in because they were over diuresed, that it is a hospitalization, but it's not a hospitalization for worsening heart failure.

ACTING CHAIRMAN BORER: Steve.

DR. NISSEN: Yeah. You know, it's interesting because we all sort of seem to flag the

same points when we reviewed this, and I also was a little bit uncomfortable. Let me make sure I understand this.

A patient that came in at 6:00 a.m. and went home at midnight, came in with symptoms of some kind, was not adjudicated as heart -- it could not have been a heart failure admission.

DR. COHN: No, they were adjudicated, and they were counted as a more than four hour stay out of the hospital.

DR. NISSEN: Well, I'm just reading what the FDA reviewer said. It said, "Hospitalizations that were clearly less than 24 hours were not submitted as events." That's what the book says. Now, is that right or wrong?

DR. COHN: Bob, can you clarify what happened with those events which were more than four hours in an intensive care unit?

DR. GLAZER: Again, if the information, any information concerned that it was a cardiovascular event, it went to the endpoint committee. How the endpoint committee classified it if they wanted to classify that as a hospitalization for heart failure, they made a definition that it had to be an overnight stay.

DR. NISSEN: So that would not have been a hospitalization for heart failure no matter what?

DR. GLAZER: From my understanding.

DR. NISSEN: Okay. So the FDA reviewer was correct there. I'm puzzled by the rationale for that, that's neither here nor there.

DR. COHN: Well, you have to have a definition for hospitalization.

DR. NISSEN: Sure, but you know, what it means is that a 12 hour hospitalization that occurred from 9:00 p.m. to 9:00 a.m. was a heart failure admission, and one that occurred, you know, from 9:00 a.m. to 9:00 p.m. wasn't. I mean to us that seems bizarre.

DR. COHN: But they were captured by the four hour criteria. So they all come out as a primary endpoint. There's no distinction made between primary endpoint from hospitalization and for four hours or more in an intensive care unit.

DR. NISSEN: No, no. But I'm saying somebody didn't come into an intensive care unit. They came into, you know, a hospital ward, you know, for an 18 hour admission. If that admission did not have an overnight stay, it would not have been a heart failure admission.

DR. GLAZER: And again, they would have had to receive from my understanding four hours of an IV inotrope during that, and that met the criteria. So I think, if I recollect, the problem was collecting the times, and the dates were collected, but the times were not clear on many of the cases.

So I think for adjudication purposes, change in date was a criteria for calling it overnight stay.

DR. NISSEN: yeah, I understand where we're coming from, but so we all understanding each other, you could come in at nine o'clock in the morning, and you could spend the day getting large boluses of intravenous furosemide to get you out of heart failure and go home at 9:00 p.m. that night, and that would not have been a heart failure admission.

DR. COHN: But it would have been captured as a four hour or more stay with aggressive intravenous therapy.

ACTING CHAIRMAN BORER: I think you've got to have an inotrope, Jay.

DR. COHN: No, no. It doesn't say inotrope. It says --

ACTING CHAIRMAN BORER: It does in our briefing book. So we've got some confusion here --

DR. COHN: Oh, really?

ACTING CHAIRMAN BORER: -- that we need to sort out.

DR. NISSEN: That patient that I just defined --

DR. COHN: Here. Let's just remind you of the morbidity endpoint.

DR. NISSEN: I mean, my reading of the book, and you're going to have to tell me if I'm wrong, is that a 9:00 a.m. to 9:00 p.m. admission getting a bunch of intravenous furosemide for a patient with pulmonary edema would not have been heart failure by this definition.

DR. GLAZER: That was my understanding.

DR. NISSEN: Okay. Now, you know, it may not have made any difference, but it doesn't seem very logical to me, I must tell you.

ACTING CHAIRMAN BORER: Can you tell us, just so we can put this into context, how many patients would have fallen into the category that Steve is talking about?

I mean, you know, this was a big study. If the number of patients not captured under this particular definition is relatively small, we can probably just, you know, move on, but do we know what

the numbers are?

DR. COHN: Well, if we didn't capture the data, the endpoint committee would know. And I'm sorry that Peter is not here yet, and hopefully he will show up because he's the one who processed all of these, and all of those data would have been provided to him.

If a patient was in the hospital from 9:00 a.m. to 9:00 p.m., they would have gotten that data as an event, and then they would have decided what to do with it.

Now, my understanding is that they used the overnight stay as a criteria for hospitalization, and I guess we could ask him in how many instances they reviewed a case that didn't meet the overnight stay, but actually didn't get captured at all because they didn't by chance get nitroglycerine or nitroprusside or something and got IV diuretic.

We'll try to ask him when he comes. My understanding is it was almost zero that didn't meet the criteria.

DR. NISSEN: Can I just tell you? I mean, in our institution patients come in all the time, and they come into the emergency department. They will come in in the morning, and they're in pulmonary

edema, and they have known severe heart failure. They're put in a short stay unit. They get IV diuretics to get them out of pulmonary edema, and they go home the same day.

DR. COHN: Well, they probably get some IV nitroglycerine, too, which would make them eligible for the four hours, and we can ask --

DR. NISSEN: I actually wish they did, Jay, but they don't always.

DR. COHN: Yes.

DR. NISSEN: And so just to me it's a hole here that I think -- I mean, I just want to make sure I understand it well.

There's a reason why you're getting a lot of discomfort here, and I'm going to just speak for myself and tell you why we're --

MR. MacNAB: I just want to make it clear that --

ACTING CHAIRMAN BORER: Could you use the microphone?

DR. COHN: Use the microphone, Malcolm.

MR. MacNAB: I wish Peter was here, and we can get any additional information you want, maybe not today, but we can get it for you.

I think the real problem -- I remember

discussing this with him -- was we wanted to be consistent, and we wanted to be accurate, and the worst thing would have been to improperly classify people and without the times, which were not consistent. The most consistent thing was the date.

And, again, it was randomized. It was blinded, and I think the decision of the endpoint committee was made to do it right and not make mistakes.

ACTING CHAIRMAN BORER: Can I just make one --excuse me one second, Steve.

Just to clarify this further, my understanding is that the data indicate that valsartan was more effective than placebo on top of background for all morbid events combined. That was driven predominantly by the hospitalization, but it was true for all morbid events combined, which would include the hospitalizations, and the non-hospitalizations.

DR. COHN: That's right.

ACTING CHAIRMAN BORER: Is that correct?

DR. COHN: That's correct. That's correct.

ACTING CHAIRMAN BORER: I mean, that may put this in a different context perhaps.

DR. COHN: I've given you the

hospitalizations separately to show the 27.5 percent reduction, but the primary endpoint was all the events combined, and I, frankly, believe -- and I can't -- Peter would have to verify this -- but I believe the number of events that were not captured because of these rules is almost zero because the committee was very attentive to every event, and they reviewed all of these events.

And if they had excluded a patient who was getting boluses of diuretic every hour for 16 hours and came in at nine in the morning and went home at midnight, and it didn't count as a hospitalization, they would have been as disturbed as you are actually, Steve. So I think they --

DR. LINDENFELD: Jeff.

ACTING CHAIRMAN BORER: JoAnn.

DR. LINDENFELD: I think JD-3 -- I think the only things that were included were if you got an inotrope or vasodilator for more than four hours. I don't think the kind of admission that Steve was describing would have been included in more than --

DR. COHN: Well, that's right, but what I'm saying, JoAnn, is I don't think there were many, if any, of those events that would have influenced the result, but we'll check with Peter.

DR. NISSEN: See, we don't know, and the reason we don't know is I'm going to read you what the FDA reviewer says. "Hospitalizations that were clearly less than 24 hours were not submitted as events." Therefore, if they're not submitted --

DR. COHN: No.

DR. NISSEN: -- then they're not adjudicated.

DR. COHN: No, no, that's not true.

DR. GLAZER: That's not correct.

DR. COHN: They were submitted, and then --

DR. GLAZER: And that's what we have in our briefing book.

DR. COHN: But the process that we used was outlined by Dr. Glazer. Essentially most everything, unless it was very obviously, you know, a patient was admitted for plastic surgery or something, and then that would have been listed, and the endpoint chairman could have asked for that if he wanted.

But all of those types of events you're talking about would have been listed for him, and I believe, Dr. Cohn, the number of the types of patients you're talking that came into the ER for what we would call a little tune-up of IVs is not that great, but I

can get you the -- I will get you those numbers for you.

DR. NISSEN: I guess the reason that a lot of us are uncomfortable is that we would have preferred an independent adjudication process, and when we read about a process where the company is submitting, selectively submitting events to a committee, as opposed to a committee that reviews everything, it makes me uncomfortable. I guess that's the problem.

DR. GLAZER: Well, I can assure you it was done. Every event or every possible hospitalization, the listing of what it was was available to it, and most of the hospitalizations for this type of patient are obviously cardiovascular. I believe it was pretty independent, and I think when Peter is here, I think he will say the same thing.

DR. COHN: And it was all blinded, Steve. So I mean, there was no --

DR. NISSEN: I understand. I understand.

MS. TARGUM: I just want to point out that the information the agency received was relied upon in the manual.

ACTING CHAIRMAN BORER: Okay. So it sounds as if from the definitions that we have here

that if you got inotropes or vasodilating agents for four hours, that would be included. But if you just got diuretics, that wouldn't be included, and that may not be correct in practice.

So we'll have to wait for the endpoint committee to clarify that for us.

JoAnn and then Alan.

DR. LINDENFELD: Just to come back to this adjudication process, I understand that from trial end to trial completion there was a difference of from 906 to 975 deaths. My question is: how many additional heart failure hospitalizations were there in that same period of time?

And our briefing book suggests that the deaths and the hospitalizations between that period of time, trial end and trial completion, were not adjudicated; is that correct?

I guess I wonder how many of them that is.

DR. COHN: No, everything was adjudicated up until the final -- I'm sorry. I didn't quite hear your point, JoAnn.

DR. LINDENFELD: Well, our booklet says that between trial end and trial completion there was a difference of from 906 to 975 deaths. It says there was no adjudication on mortality/morbidity endpoints

at trial end.

DR. COHN: No, that's not correct. The 906 was the number of reported deaths. When the DSMB met, identified that it had passed the 906 point, and recommended that the study be terminated. That recommendation goes to the sponsor. The sponsor makes a judgment with the steering committee to terminate the study, sets a date for termination, and then many more deaths are still being reported during that period of time.

All the events that occurred until the end of the trial were adjudicated by the committee, everyone.

ACTING CHAIRMAN BORER: Alan.

DR. GLAZER: Can I just clarify? Robert Glazer from Novartis.

The events that occurred from May 3rd to the end of the trial were not adjudicated.

DR. COHN: But you don't mean by the end of the trial. You mean by -- the trial ended on --

DR. GLAZER: May the 3rd, and that's when the 906 deaths we were made aware of, and that was the day that the trial was considered completed. Subsequent to that, bringing in the last patient for last visit for follow-up to conclude, officially

conclude, the trial, there were events that occurred. Those events were not sent to the endpoint committee because --

DR. COHN: And they aren't counted --

DR. GLAZER: And they are not counted.

DR. COHN: -- in our analysis either. The analysis is as of May the 3rd when the trial ended.

DR. LINDENFELD: Is the analysis on 906 or 975 deaths?

DR. COHN: Nine, seventy-five.

DR. LINDENFELD: Well, but then that difference between 975 and 906, those were the number that were then not adjudicated, and I assume there's a similar percentage of --

DR. COHN: No, no.

DR. LINDENFELD: -- hospitalizations.

DR. GLAZER: I'm sorry. There was a certain number of events that occurred from when observed the 906 deaths. When we observed the 906 deaths, obviously when we collect documentation afterwards, there were additional people who had an event, a morbid event or a mortal event that hadn't been reported to us or was in the process of coming to us through the process.

That's what accounts for the additional

information. So those events, yes, they were adjudicated and put into the analysis. that's why it doesn't end at 906, because that was a date that we were made aware. We found these extra events as we were doing the --

DR. COHN: I mean, let's make it clear. Every event that occurred before May 3rd, which was the termination of the trial, were adjudicated. Now, other people had events, and then they have to be brought back, and they have to be told about the results of the study. They have to be taken off their study drug.

People don't go off study drug on May 3rd. They have to come back in for a visit, and between May 3rd, which was the official termination of the trial, and the time that they came back and were taken off of their study drug, there were events that took place, but they weren't part of the trial. That was post trial, and they're not counted in any of the analysis that we've shown here.

DR. FLEMING: May 3rd was the date of 906 deaths or 979?

DR. COHN: No, come on. You're waiting for reports to come, and when the number of reports --

DR. FLEMING: We fully understand that

between a data monitoring committee's review and when the database is finalized, additional events come in.

DR. COHN: Yeah.

DR. FLEMING: The question is very simple, and I think your answers so far seem to be confusing. The date at which the data monitoring committee met, there were 906 deaths. The reports that we've been provided --

DR. COHN: There were over. There were more than --

DR. FLEMING: -- give us 979 deaths. Presumably there were also emerging during that time frame CHF hospitalizations as well.

Simple question: is the primary analysis that we've been shown for morbidity events, were all of the CHF hospitalizations in that analysis? Were all of them adjudicated?

DR. COHN: Yes.

DR. FLEMING: Thank you.

MR. HAUPTMAN: Let me clarify -- Lawrence Hauptman, Novartis -- the 906 and the 975 number. The 906 was reported as hitting -- that was supposed to be the endpoint, that many deaths, and then it was decided that that was May 3rd, but then in going back to the field and getting all of the paper work in,

those extra 70 people were discovered in terms of deaths and also in terms of the morbidity endpoint.

But they all occurred before May 3rd. So anything that occurred before May 3rd is what you see in the data that was submitted in the analyses. Stuff that happened after May 3rd is after the trial ended and is not part of any -- you haven't seen any data on anything that happened after May 3rd.

DR. FLEMING: So, Larry, then the final updated database indicated that by May 3rd there were 979 deaths.

MR. HAUPTMAN: That's true.

DR. COHN: That is correct, and it's always true in trials. When the reports come in, you wait for the reports of the target number and then you terminate the trial. You don't terminate it the day the DSMB meets. The DSMB has to meet and make a recommendation. There has to be a date set when you're terminating the trial, and that is the date.

And at that point, by going back and reviewing every center, there were 900 and whatever it is, 70-some deaths.

ACTING CHAIRMAN BORER: Alan and Paul on this same issue, and then we'll go to Tom for a new issue. Alan, did you have?

DR. HIRSCH: Well, my question is related. Obviously our goal is to make sure that the medication if used by the public for heart failure breeds a clear benefit. So we're sort of adjudicating right here.

What I'm wondering is do we have in the room at this time data that we can look at on emergency room use by the two groups in Val-HeFT.

Sort of opinions. We love to see data.

DR. COHN: You mean by the four hour criteria for emergency room or do you mean just having to go to the ER?

DR. HIRSCH: I'll take either.

DR. COHN: Well, we showed you the -- can we go back to the slide that breaks --

DR. HIRSCH: Not hospitalization.

DR. COHN: -- breaks down the morbidity endpoint?

DR. HIRSCH: The breakdown of the morbidity endpoint.

Yes, ideally, in other words, Jay, without the use of inotropes or vasodilaters. We're looking for raw data.

DR. COHN: No, I guess those data were not captured. These are the primary endpoint data. This is the number of patients who got intravenous therapy

that were not hospitalized and met that criteria, and you can see there's only five in each treatment arm.

We really did not capture such things as patients coming to the ER not feeling well and being given an antibiotic or an extra dose of oral lasix and then going home. We did not capture that because we wanted to be rigid and maintain a very high standard for what represented true worsening heart failure or events equivalent to a hospitalization.

ACTING CHAIRMAN BORER: Paul and then Steve.

DR. ARMSTRONG: Again, Jay, I'm not trying to be difficult, but the briefing book has said that the endpoints, the morbid endpoints at least between May 3rd and the completion of last patient, last visit were recorded by the investigators and not adjudicated.

DR. COHN: That's right.

DR. ARMSTRONG: You've said that they are adjudicated.

DR. COHN: No, no. Anything after May 3rd was not adjudicated. I don't know how more clearly to say that. Everything up to May 3rd --

DR. ARMSTRONG: Thank you.

DR. COHN: -- and all the data you've seen

is everything that happened in the trial up until May 3rd. The duration in which patients stay on drug after May 3rd varies, of course, depending on when they're able to get back and visit with their health care provider and be taken off of their therapy and a decision made what treatment they're going to go on.

And there were events that took place there, and Novartis is obligated since these patients are in a protocol and they're still on test drug; they're obligated to monitor those events, but there was no purpose in adjudicating them because they were not part of the primary analysis.

ACTING CHAIRMAN BORER: Steve and then Tom.

DR. NISSEN: Yeah. Jay, I agree with you that going to the emergency room should not have been the primary endpoint in the trial. I think that the right endpoints were used. The problem that we're having is that, you know, patients with heart failure make frequent trips to emergency departments. They use health care resources to do so, and collecting the data and reporting it for purposes of further understanding the benefit and risk of the drug would have been greatly helpful to us. This is kind of a message to people who do such trials.

I mean, I can understand why you would not want to adjudicate those as a heart failure event, but what if, you know, there were, you know, more trips to the emergency department by patients taking the active drug versus the control? That would suggest that there was a general safety disadvantage to the therapy.

And so if that's not captured, we have no way of knowing about it, and that's sort of what people are saying. That's more of an editorial comment than a question because I know we don't have that data. We don't know how many patients made a trip to the ED.

The other reason for the discomfort is that if you look -- as I look carefully at the data, the risk ratio for hospitalization was substantially lower for the active treatment arm by the endpoint committee than it was by the investigators.

So in the process of going through the adjudication process, there was a -- if you go on the briefing document on page 99 for the committee members, what you see is there was a 27 and a half percent reduction from the rest --

DR. COHN: Yeah, here's the data actually, Steve.

DR. NISSEN: Yeah.

DR. COHN: These are what were defined as heart failure related hospitalizations. You can see the endpoint committee eliminated a lot in both the placebo and valsartan arm. So they were much more meticulous about the criteria for heart failure hospitalization.

And here was the endpoint committee's adjudication showing a 27.5 percent reduction and a p value with four zeros.

The investigator -- which was not the primary endpoint. Remember that the protocol said this is the primary endpoint, but if we went by the investigator assessment, there was still a significant reduction, but it was 16 percent rather than 27 percent.

DR. NISSEN: Right, and so that's why we're focusing on closely on the adjudication process, and I think you used the right endpoint. I'm not disagreeing with that at all, but I'm trying to understand why there was such a substantial difference.

I mean, the benefit of the agent was nearly twice as great if one looks at the way the endpoint committee looked at it versus the way the

investigators looked at it.

DR. COHN: I don't know. I mean, I can't answer the question.

DR. NISSEN: Yeah, I know you can't, and that's why we're being so nitpicky in understanding it.

DR. COHN: You know, unfortunately it was significant in both instances.

DR. NISSEN: Yeah, yeah.

DR. COHN: Obviously, and I've been through this many years, Steve, as you know. Investigator assessment of mechanism of death and of reason for hospitalization is seriously variable from investigator to investigator, and the reason we set up an endpoint committee is to have some uniformity in the way we will adjudicate these things.

And when you do it uniformly, you're right. I have no understanding of why there would have been a preferential effect, except that that's, indeed, what we would have anticipated, that if you use much more stringent, uniformed criteria, we'll find the benefit of valsartan.

If you just looked at all hospitalizations, which we did and I showed you that slide, the difference is not statistically

significant. So it was very important to adjudicate and to identify what is identified as worsening heart failure hospitalizations, and that's not what the investigators did.

The investigators, and many of them put patients in the hospital for reasons that weren't related to worsening heart failure, and they just checked the box that said "heart failure." And we did it much more carefully. This is very casual.

DR. NISSEN: You don't have to convince me that adjudication is important. But the trigger for many of us to look more closely at this is this fairly substantial disparity between the investigator report and the adjudicated endpoints.

DR. COHN: Well, I think the message is that it's very important to adjudicate.

ACTING CHAIRMAN BORER: Tom, and then after that we'll move on to the next topic because we're falling a little behind.

DR. FLEMING: Jay, just a quick question. You had mentioned that the trial had been powered targeting a 20 percent reduction in the mortality endpoint. Can you tell us what the targeted reduction was in the --

DR. COHN: What the target what?

DR. FLEMING: Could you tell us what the targeted reduction was in the morbidity endpoint?

DR. COHN: Well, we didn't power it for the morbidity endpoint. We knew there would be many more events, and we knew that we would be well over powered for morbidity. So there was no calculation made.

The monitoring was based upon mortality so that we powered the trial for a number of deaths to identify that mortality reduction, and the DSMB monitored mortality only, not morbidity.

MR. CHIANG: Tom Chiang, Novartis.

Yea, the sample size space on the calculation, but we did assess the potential power for the morbid endpoint also as a primary, and the powers are enlarged. You know, a certain percent reduction would have more than 80 percent power.

DR. FLEMING: Well, I don't want -- that's in retrospect. I was interested in what your prospective targeted interest was, and it was 20 percent reduction and death, and in morbidity it was clearly --

MR. CHIANG: We did not talk, as I say. As I say, sample size is based on the mortality as the Dr. Cohn mentioned. We did not, say, target which

percentage reduction for morbidity, but we did calculate barriers reduction to get a feeling to feel comfortable

DR. FLEMING: So there was no clinical sense. This was one of your two primary endpoints. There was no preplanned clinical sense of what magnitude of effect you wanted to get on morbidity, and it was one of your two primary endpoints?

MR. CHIANG: Well, we did, as I say, we did try to calculate there as possible. So we tried to insure --

DR. FLEMING: Good. So what were those various possibilities? What were they?

MR. CHIANG: As I say, beyond ten percent we assess all possible power, and for 13 percent because that just give you an idea what is power calculated for.

DR. FLEMING: So when the study was planned, you had planned a 13 percent reduction in morbidity?

MR. CHIANG: It's not planned for that. We calculated various case to feel comfortable. If this case happen, we do have sufficient power.

ACTING CHAIRMAN BORER: Okay. Maybe we can move on to the safety data, and we'll get back to

any other clarifications a little later.

DR. COHN: We've got to go into the subgroup stuff first.

ACTING CHAIRMAN BORER: Oh, sorry.

DR. COHN: That comes next.

PARTICIPANT: Unless you don't care about the subgroup.

ACTING CHAIRMAN BORER: No.

DR. COHN: If you want to disregard it, we'll just disregard it, but --

ACTING CHAIRMAN BORER: It's your presentation.

DR. COHN: Okay. Now, as you're all aware, when one does a large scale trial like this, one often assesses subgroups to convince oneself that there is homogeneity among various groups because we're dealing with a very widely divergent population. So it's one of the dutiful things that we all do to look at this kind of a plot of the primary endpoint which was favorable, the morbidity endpoint, and we look at a number of baseline demographics, for instance.

This was the point estimate and the confidence intervals for the overall study favoring valsartan. This is in younger and older patients.

This is in males and females. This is in whites and blacks. And you'll notice the only point estimate that goes to the right of that line is the black population. It's only a modest size population and with very wide confidence intervals, but we certainly were unable to convince ourselves that we had demonstrated efficacy in the black patients in this study.

This was the other racial groups. This is the U.S. and the non-U.S. So pretty close consistency for all of these groups.

Now, what about etiology of disease and severity of disease? Here was ischemic heart disease and those without ischemic heart disease. Here are diabetics and non-diabetics. Here's New York Heart Class II and III and IV. Here's ejection fraction above and below the median of 27. Here's ventricles smaller than and larger than the median ventricular size, you know, and for the most part there seems to be no striking difference among these groups.

Yes, maybe those with less severe heart failure, that is, a higher ejection fraction and smaller hearts, don't exhibit quite as much benefit as those who have more severe disease, but that's not terribly surprising.

So no inconsistencies.

However, there was a clear baseline difference in therapy, and it's really appropriate to look at background therapy using an angiotensin receptor blocker on top of ACE inhibitors and beta blockers, mandated that we look at that, as to whether that's influencing outcome, and of course, that's not a continuum. That's a yes/or.

What drug were you on at baseline? And this is the analysis that we did. Now, this was not preordained, and we did stratify for beta blocker use. I didn't point that out in the methods, but we did stratify for beta blocker use with an intent to make certain that we had an equal distribution of beta blockers in the two treatment arms, not because we expected necessarily any interaction.

We didn't stratify for ACE inhibitor, but 93 percent of the patients were on an ACE inhibitor. But it is a yes/no answer. So what about the patients who were not on an ACE inhibitor? There were 366, and you can see that this favored valsartan. This is mortality now, not morbidity. This is the mortality issue, and I show that for a really distinct reason.

So in mortality there appeared to be a trend here for a benefit of an ACE inhibitor. Those

patients getting an ACE inhibitor, okay, close to the line. Those patients not on a beta blocker here, those patients on a beta blocker favored placebo, and that appeared to not overlap neutrality here.

Now, this is mortality. We did not find a benefit on mortality. So looking at these subgroups is perhaps not entirely appropriate, but we felt it important to do it, and we seem to see a clear trend for a benefit on mortality in the patients not on an ACE inhibitor, and a worsening mortality in those receiving a beta blocker.

But then we realized, well we have to look at this in more detail because there are four subgroups. There are those who are neither an ACE inhibitor nor a beta blocker, and here was their point estimate.

There are those who are on an ACE inhibitor, but not on a beta blocker, and that's their point estimate. There's those on a beta blocker but not on an ACE inhibitor, and here is their point estimate favoring valsartan, and there are those who are on both ACE inhibitor and beta blocker, and this is the group that seems to exhibit a worsening mortality with a risk hazard ratio of over 1.4.

Now, the interaction p value for overall

interaction p value is .0091, and Tom knows better than I, but it's kind of hard to get interaction p values of that significance. So we thought this was something we really couldn't disregard.

Now, let's look at the morbidity, which was the endpoint favorably affected by valsartan. Now, here you've got the patients not on an ACE inhibitor, highly significant benefit. Even the ones on an ACE inhibitor you can see their confidence interval just touches the neutrality line.

Here are patients not on a beta blocker. here are those on a beta blocker, the trend in the wrong direction, and when we look at the four subgroups now, those on neither neural hormonal inhibitor, risk ratios down close to .5; those on an ACE inhibitor not on a beta blocker, still a highly significant benefit of valsartan; those on a beta blocker but not on an ACE inhibitor, there are only 140 of them, but clearly the point estimate trending favorably toward valsartan; and those on both background drugs, point estimate clearly on the placebo side.

And here the interaction p value was .0011. So can we disregard this? Well, we can't for two reasons: one, that there is this highly

significant interaction, and it's not terribly surprising.

And, second of all, there's the safety issue because on mortality, the group taking both an ACE inhibitor and a beta blocker exhibited a statistically significant worsening of mortality.

So we felt we could not at all disregard this subgroup analysis.

Now, this is the actual data, which may help you a little bit in the same four major groups, and then the four subgroups formed by the use of the one or both drugs, and here you can see on morbidity here that the p value favoring valsartan was highly significant in all three groups except the one taking an ACE inhibitor and a beta blocker, where the trend not only went in the other direction. The p value wasn't significant, but it was trending adverse.

So these three groups all exhibit by themselves a significant reduction of morbidity.

Now, these are all data based on administration of drugs at baseline. How close does this correlate with the maintenance of these drugs during the study? Because that's of importance. And this data attempts to show you that.

Of the patients on an ACE inhibitor at

baseline, 90 percent were still taking the ACE inhibitor at the end of the study. On those with a beta blocker, 92 percent were still on the beta blocker at the end of the trial. That's true of all the drugs except spironolactone in which there was a reduction of the use of the drug by the end of the study.

In those patients not on the drug at baseline, only 16, 13 percent went on the drug during the trial. More patients who were not on a diuretic started diuretic during the trial, which is expected because heart failure worsens, and they then finally required diuretic.

I find it surprising that 12 or so percent or 15 percent of the patients weren't on a diuretic even at baseline because heart failure almost always requires a diuretic.

So pretty good congruence between what the therapy was at baseline and what the therapy was at the end.

Well, one of the groups we said at the beginning we wanted to look at because there are no data available in the literature prospectively is the group not on an ACE inhibitor. Now, a third of these people were on a beta blocker, but they were not on an

ACE inhibitor, and one of the important questions is: is valsartan a substitute for an ACE inhibitor in patients who don't tolerate an ACE inhibitor.

So this was only seven percent of the population, 370 patients. This is the mortality curves which separate pretty early and widen over time. That's a 33 percent reduction in mortality. The p value is .017.

Here is the morbidity in that population. A 44 percent reduction of morbidity, the curves really widen out over time. The p value here is 002. It's only 370 patients, but it's the first demonstration prospectively that I know of that one can use an ARB, specifically valsartan, and exert the kind of favorable effect we've associated with ACE inhibition.

Now, we also wanted to look at all of the secondary endpoints to see if they were congruent with our clinical outcome data, suggesting that that one subgroup didn't do very well. Now, these are independent measurements. They have nothing to do with hospitalization or death. These are completely independently measured secondary endpoints.

This is left ventricular ejection fraction, and here are the four subgroups if you will, people taking neither an ACE nor a beta blocker, those

taking an ACE inhibitor, not a beta blocker, those taking a beta blocker, not an ACE inhibitor, those taking both.

You will notice that although this group was very small, there was certainly a trend for much greater benefit of valsartan and placebo on ejection fraction. This group highly significant, this group highly significant.

Ah-ha, here's our little culprit group. No benefit on ejection fraction.

If we look at just the groups leaving that group out, the difference is highly significant, and let me show you that.

Here then is the ejection fraction change in the patients who are -- based upon their use of beta blocker, ACE inhibitors. Here was the overall EF change, .00075, benefitting valsartan -- favoring valsartan over placebo.

Here are the group getting both a beta blocker and an ACE inhibitor, the absence of a benefit. If we take that group out and look at the other subgroups, the benefit goes up to .00002 on ejection fraction.

Here is left ventricular internal dimension by echo. You'll see a benefit here, a

benefit here, a benefit here, all three subgroups exhibiting a significantly greater reduction of their ventricular size with valsartan compared to placebo. Here is our culprit group. No difference.

So here was the overall effect on left ventricle. Here is the lack of effect in that subgroup, and actually a greater difference now in this smaller group that excludes this one group over here.

Here is the living with heart failure score, independently measured by the patient. Nobody has intervened to influence them.

Here's the benefit in this group, this group, and this group, all of them exhibit rather striking greater worsening of heart failure in the placebo than the valsartan group.

Here is our culprit group. No difference. If we take that group out, the difference gets even greater, and I'll show that in the next slide. Here it is.

Here was the overall benefit on living with heart failure score. Here is the lack of benefit in that one subgroup, and here is the benefit on the residual patients now with a Z of 0002 p value.

What about New York heart class? The same

thing is true. There was overall a benefit of valsartan compared to placebo, more improvement, less worsening.

This group over here, no benefit. When you take them out, the p value goes to 000003.

Now, what about the overall mortality? The mortality overall we said neutral, heart risk ratio of 1.02. Here was the risk ratio in the group taking both an ACE inhibitor and a beta blocker, 1.4, which was statistically significant in that subgroup.

When we take that group out, now we're seeing a trend for a favorable effect on mortality, a risk ratio of .92. So beginning to bring out what might be a favorable effect of valsartan even on mortality, obviously way under powered to pick anything up, but there it is.

And what about morbidity? Well, the morbidity --

DR. FLEMING: Could you clarify, Jay, when you said "way under powered," go back to that slide?

DR. COHN: Well, I said we were under powered to pick up an eight percent difference, which is what that slide showed.

DR. FLEMING: Oh, okay. It's not under powered to pick up a meaningful difference. It's

under powered to pick up a really small difference because most --

DR. COHN: Well, I don't know what --

DR. FLEMING: -- you've got 30 --

DR. COHN: I would object to your use of the word "meaningful."

DR. FLEMING: -- three hundred patients in that subgroup.

DR. COHN: I think an eight percent reduction in mortality is probably meaningful.

DR. FLEMING: The study was targeting a 20 percent reduction.

DR. COHN: That's right. Yeah. I'm saying we're under powered to pick up the difference that we found.

DR. FLEMING: Well, let's come back to this. Keep going.

DR. COHN: Okay. And now, this is the morbidity endpoint. Remember that the p value for our primary endpoint was .009. In that one subgroup, the trend was in the other direction, the p of .104, and when we take that group out and look at all the other subgroups now, the p becomes 00003, and the risk ratio is reduced to .785.

So we now have to cope with this subgroup

that we can't disregard, and in fact, if we think this is an important subgroup that should not receive the drug, and I do believe that that is the case today, until more data are accumulated from other trials, and we say these patients we're not going to treat, we're left with the rest of the patients in whom the statistical significance of the data is far more dramatic.

So in summary, I believe that we can conclude that the benefit on morbidity that we've observed in the overall trial was seen particularly in patients on neither ACE nor beta blocker or on ACE inhibitors or beta blockers, but not in those patients receiving both drugs.

Thanks.

ACTING CHAIRMAN BORER: Any clarification of fact questions for Jay on this section?

No, sounds like you -- oh, you do. I'm sorry, Tom. Go ahead.

DR. GLAZER: We also do have Dr. Carson who has joined us if there's further questions for him.

DR. FLEMING: Actually I'll wait until the end.

ACTING CHAIRMAN BORER: Do you want to

hear from Dr. Carson about the unresolved issue here?

DR. COHN: Perhaps we do. Steve?

DR. NISSEN: Shall we go back or do you want to go forward? Do you want to talk about this part or do you want to go back to --

ACTING CHAIRMAN BORER: Well, why don't we start with this? And then we'll go back and test the other.

DR. NISSEN: Okay. Jay, there was another breakdown that I didn't see in there that I'm actually very interested in, and that was the U.S. versus non-U.S. Clearly there was a much greater benefit almost across the board in the non-U.S. population, and I wonder if you would help us understand that.

DR. COHN: Yeah, let's look at that. This is the morbidity and mortality in the U.S. and non-U.S. populations, and although the hazard ratio was, indeed, a little -- it was different here. Of course, this is mortality, not morbidity. This was our primary endpoint in which the non-U.S. had a slightly lower hazard ratio than the U.S., but the confidence intervals are really almost entirely overlapping.

And for first heart failure hospitalizations, again, there is a difference, but once again, the confidence intervals are really

overlapping. The interaction p value is very high.

So I think there is no real geographic -- evidence for a geographic difference here.

DR. LINDENFELD: The percentage of patients on beta blockers in the U.S. and non-U.S., is there --

DR. COHN: Very close to the same. It was a little higher in non-U.S. than in U.S., but they were both within the 30 percent range.

DR. NISSEN: Yeah. Actually the data here are slightly different from the data that we have from Dr. Targum's review, but in the FDA book, CHF hospitalization, the risk ratio in the U.S. was .81 and the risk ratio in the non-U.S. was .67. You know, from .81 to .67.

I asked the question, and I'll tell you why I asked it, Jay. This has got to be the fourth or fifth trial I'm aware of, major, mega trial where the benefits were substantially greater in the non-U.S. population than in the U.S. population, and it's something that has been troubling many of us because obviously this agency regulates the use of drugs in the United States.

And I have my own hypotheses here, which maybe later on we can talk about, but any insight here

would be useful because there really does appear to be an across-the-board difference if you look carefully at the data in the U.S. versus non-U.S.

Any insight?

DR. COHN: Well, I mean, we've obviously thought a lot about this. I think it was far more pertinent in a previous trial where this became a major issue, as you know.

There is a somewhat higher incidence of hospitalizations in non-U.S., which probably reflects the health care system and much resistance in the United States for hospitalization. So one possible explanation would be you're more likely to be hospitalized when you're in Europe, and therefore, a benefit of therapy might be more demonstrable in the European population. It might be a more sensitive marker.

Many have raised the issue of African Americans because you can see from this data, and you know that I've had a great interest in possible differences based upon African American and white patients, and one possible explanation is the impact of African Americans, but in this trial I think the number was too small to impact on that.

So we don't have any rational reason for

seeing a difference. Genetically there's not a major difference between Europe and the United States. So I must say that I don't have a good answer to that.

ACTING CHAIRMAN BORER: Tom.

DR. FLEMING: Just a couple of questions. Jay, in your introduction, you had given some of the motivation for the interest in valsartan in the context of what you might already be able to expect to achieve with ACE inhibitors, and in the briefing document, the sponsor has indicated that the combination of angiotensin receptor blockers and ACE inhibitors may be synergistic by providing the more complete inhibition of the renin angiotensin system through the blockade of the AT-1 receptor, which was exactly the presentation that you have given.

If we look then, in particular --

DR. COHN: I don't think we used the term "synergistic," but okay.

DR. FLEMING: This is exactly a quote. I'm quoting exactly your briefing document.

DR. COHN: Does it say --

DR. FLEMING: "May be synergistic."

DR. COHN: Well, I guess I'd argue about that.

DR. FLEMING: Looking at your data

specifically in the group of patients that were on ACE inhibitors, which was 92 percent of the population, when you look there, what you find is an eight percent reduction in the morbidity, but a seven percent increase in mortality.

Essentially then do these data fairly strongly argue against a synergistic effect in the presence of an ACE inhibitor?

DR. COHN: Well, in the absence of beta blocker, now, you can't talk about ACE inhibitors any longer without bringing the beta blocker in because it's another neural hormonal inhibitor. In the absence of a beta blocker, the efficacy of ACE inhibitor, of valsartan on top of ACE inhibitor was greater than that in terms of the morbidity endpoint, and that represented the largest segment of the population, two thirds of the patients.

So I don't think you any longer can look at a subgroup saying ACE or no ACE when there's a beta blocker in a third of the patients who are on the ACE inhibitor or not on the ACE inhibitor.

Do I think that there's a synergistic effect? I think that's a term that -- that's a pharmacologic term that I'm very hesitant to apply to this, and I guess I had missed the fact that that word

was used in the briefing document.

"Additive" would be the word that I would have used, and I believe we have demonstrated an additive effect, and that would be the only word I would have used in describing our proposal.

DR. FLEMING: But you only argue that by subdividing out those people who were also on a beta blocker. That's your answer. Your answer is, yes, you believe it's additive, but only by subdividing or eliminating those people who also received a beta blocker.

DR. COHN: No. The question is: does adding valsartan to an ACE inhibitor have an additive effect?

DR. FLEMING: That's correct.

DR. COHN: We know it has an additive hemodynamic effect. That's been studied in 103 and 104. We know it has a neural hormonal effect. That was studied in 104, and it's also been studied in 107.

The question is does it have additive benefit on morbidity and mortality, and the answer --

DR. FLEMING: On your primary endpoints, correct.

DR. COHN: On the primary endpoint.

Well, on mortality we haven't shown an

additive benefit. So at the moment we can't say that it has.

Does it have an additive benefit on morbidity? Yes, it clearly did, especially when one takes out the beta blocker group.

DR. FLEMING: Not especially when. Only when.

DR. COHN: Well, the point estimate favored here, I mean, and let's look at those patients on an ACE inhibit. The hazard ratio is .9, and the p value is .096.

Now, you can argue whether that means we did or didn't have an effect, but we have produced a ten percent reduction of morbidity when you add an ACE inhibitor to valsartan regardless of beta blocker use.

Now, ten percent reduction of hospitalization rate is not infinitesimal. It's not small. It's fairly substantial when you think of the number of hospitalizations.

DR. FLEMING: I'll go back to what I said before, and I'm quoting from the FDA briefing document on pages 102 and 103. "If you look at morbidity, the relative risk given there is .92." You're giving it as .90, but an eight to ten percent reduction in morbidity with use of ACE inhibitors, but a seven

percent increase in mortality.

So the same magnitude of mortality increases you see in reduction in morbidity when you look at the biggest group of patients in the trial, which are those on ACE inhibitors.

ACTING CHAIRMAN BORER: Jay, can I --

DR. COHN: Well, I can -- can we put up the mortality slide, the comparable --

ACTING CHAIRMAN BORER: Jay, before you answer the question --

DR. COHN: Yeah.

ACTING CHAIRMAN BORER: -- let me just introduce a concept that I'd like you to deal with as you respond to this.

You know, there were background ACE inhibitor therapy, but the doses varied. There certainly is no suggestion that background therapy was titrated to maximally tolerated dose of ACE inhibitor. Different ACE inhibitors were used, one and on and on. You know, you can response, and you should respond because the question was asked, but it seems to me that we don't have a data set that allows us to discuss whether an angiotensin receptor blocker is additive to ACE inhibitor because the trials weren't set up to answer that question.

All we can say is that in this population getting these number of drugs at these number of doses, when you added valsartan and there wasn't a beta blocker on board, that we see this.

I mean, is that a reasonable --

DR. COHN: Yeah, I showed you the mean dose of ACE inhibitors used, which, you know, is like 18 milligrams a day of lisinopril. so that on average it's close to target dose.

Is there a differential response based upon how much ACE inhibitor the patient is getting? You know, you get into very --

DR. FLEMING: Sure.

DR. COHN: -- small subgroups, and this is --

DR. FLEMING: You just can't answer that.

DR. COHN: -- the analysis we plan on doing, but all we're saying is this is the kind of -- this is good therapy. I think if you went to the community at large, the dose of ACE inhibitor would not be that high. This is the best doctors in the world treating patients the best way they know how.

Now, if you add to that valsartan, do you further improve the outcome? The answer is yes, with the provision that there seems to be one subgroup that

doesn't get benefit.

Now, the mortality, the issue that Tom raised -- can we go back to that mortality slide? Because you raised this, and I want to show you the data.

This is those same subgroups based on mortality, and what Tom is saying is that there was a 1.055 hazard ratio on mortality when you or on an ACE inhibitor. However, when you go down here and you look at the group that was on an ACE inhibitor and a beta blocker, it's 1.42. When you look at the group that was on an ACE inhibitor without a beta blocker, it's .959.

So the adverse trend here, which is clearly not significant -- it's a five percent increase -- appeared to be entirely related to this group that was also taking a beta blocker.

DR. FLEMING: Yeah, in the briefing document we have on page 103 ACE inhibitor use, all cause mortality, relative risk of 1.07, numbers similar to, but not exactly the same as what you have.

DR. COHN: Yeah. I'm not sure. I guess the --

DR. FLEMING: And so if you're looking at all of the ACE inhibitor patients, there is a seven

percent increase. As you point out, if you further subdivide, and that is controversial, those on beta blockers would have a 42 percent increase. Those off would have a four percent or six percent decrease.

DR. COHN: Right, and the numbers to make that -- I suppose we should clarify. Perhaps somebody from the FDA should clarify why their numbers in the briefing document differ from ours.

I believe it's they did not use the covariates in doing the analysis which were prescribed in the protocol to adjust for covariates. Maybe we could hear from the FDA.

MR. HUNG: Jim Hung, FDA statistician.

The number I have is unadjusted as a ratio because the primary test for all these primary endpoints, morbid events, are low rank tests, and so, therefore, I try to be -- try to use the numbers to be consistent with the test.

The sponsor's numbers are adjusted for the covariates. That's the difference.

DR. COHN: This was in the protocol, prespecified adjustments of covariates and the Cox regression --

DR. FLEMING: And this is a peripheral issue. The main answers are the same.